REMARKS

I. Status of Claims

Claims 4-16 of the claims are withdrawn.

Claims 1-3, 17-19 and 21-22 are pending.

II. Meola et al. Does not Anticipate Claims 1-3, 17 and 21 Because Meola does Not Teach all the Claimed Elements.

Claims 1-3, 17, 21 were rejected under 35 U.S.C. § 102(b) over Meola et al.

Because claim 1 is an independent claim and claims 2-3, 17, 21 depend on claim 1, what holds below for claim 1, holds for all rejected claims.

Meola does not anticipate claims 1-3, 17 and 21 because this publication does not teach all the elements in the pending claims, as required by case law.

As discussed during the interview of April 13, 2005:

Claim 1	Examiner's Comments Re Meola et al.	Arguments Against 102,103
1. A plurality of immunogenic peptides of a target protein, said peptides which produce a disease or condition specific immune response in a host, wherein the target protein is causative of, or associated with, a targeted disease or condition, and said peptides comprise the following structure:	1. HbsAg is the target protein.	
(a) from 5 to 10 amino acids in length;		FIG. 1 shows a "chimeric protein p III harboring the mimotope extra- sequence at its amino terminus" (p. 3163. col. 2) (similar with ferritin, HBV). There are no peptides taught by Meola that are 5-10 amino acids in length. The nine amino acid sequences in the FIG. 1 box are part of fused proteins (21 amino acids in length).
(b) an amino acid sequence which is identical to a contiguous amino acid peptide region of the sequence of a protein designated the target protein;	2. HbsAg sequence 120-132 is the selected peptide which is identical to a contiguous amino acid peptide region of the HbsAg (See gray overlapped area; first one).	No amino acid sequence of a mimotope in FIG. 1 is identical to HbsAg sequence 120-132. Position 120-132 **is** HbsAg. The examiner, not Meola, "selected" this peptide. There is **no** delineation of this sequence by Meola. Anyway, it is 12 amino acids in length, not fulfilling 1(a).
(c) a net hydrophilic structure as determined by the amino acid sequence of the peptide, said structure located on the surface of the target protein;	4. Both Mimotope 13 and 35 have a net hydrophilicity nature on the cell surface.	
(d) an amino acid net sequence homology of 50 percent or less as compared with contiguous amino acid sequences of a part of a comparative protein wherein the part is of the same length as the peptide.;	3. Mimotope 13 and 35 are the selected immunogenic peptides as the comparative proteins from phage library. 5. Both Mimotope 13 and 35 have less than 50% net homology compared to the selected HbsAg.	A peptide satisfying 1(a) (b) and (c) is then tested against other peptides of the same length, that is, from "comparative proteins", **not** from the target protein. This is to eliminate peptides that cross react with non-target proteins. The examiner, not Meola, decided mimotope 13 and 35 are "comparative proteins." This term never appears in Meola. A peptide that is a "comparative protein" would not by definition be one of a plurality of peptides of claim 1. These are not naturally occurring so would not cause cross-reactivity in biological samples.
(e) an amino acid sequence wherein no more than three contiguous amino acids are identical to contiguous amino acids of a part of the comparative protein matched for	6. The selected HbsAg has no more than three contiguous amino acids that are identical to the contiguous amino acids of the comparative Mimotope 13 and 35.	In addition to the selected peptide not being more than 50% homologous, no more than 3 contiguous amino acids are identical. Assuming HbsAg is equivalent

Claim 1	Examiner's Comments Re Meola et al.	Arguments Against 102,103
overall homology less then 50%; and		to the "target protein," HbsAg would not be compared here, a 5-10 amino acid peptide from HbsAg would be.
(f) an antigenic profile which elicits an immune response specific for the target protein as determined by results of immune cell proliferation assays or immunoassays of targeted disease or condition positive biological fluids compared to disease or condition negative biological fluids.	Meola et al. also teach immunizing rabbit and mice to test the immunogenic response, e.g. HbsAg antibody associated with Hepatitis B, from the fluids (serum) of the infected and control animals (See page 3164, right column, Sera assays).	Meola does not teach a peptide of 5-10 amino acids in length, that provokes an immune response to HbsAg. " In mice, mimotopes 13 and 35 optimally elicited specific anti HbsAg Ab if they were presented to the immune system on the phage coat protein pVIII (Fig. 3A, black bars). Mice were poorly immunized by mimotopes 13 and 35 if presented either as fused to ferritin or as MAP." p. 3165

An anticipating prior art reference should disclose ***each and every limitation of the claim*** expressly or inherently. *Akamai Techs. v. Cable & Wireless Internet Servs.*, 344 F.3d 1186, 1192 (Fed. Cir., 2003). To anticipate a claim, ***a reference must disclose every element of the challenged claim*** and enable one skilled in the art to make the anticipating subject matter. *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) *(emphasis added)*.

The examiner tries to force elements of Meola to match elements of the pending claims, but the matches are incorrect (see page 2, par. 2 of the Office Action). The examiner continues to try to force equating "mimotopes" with the peptides of the present invention, but there is no fit.

Meola's stated goal is "To test if these mimotopes could be useful in developing a vaccine against human hepatitis B virus (HBV)." (p. 3162) Meola's conclusion refers to mimotopes "identified from random peptide libraries...could be important leads for the derivation of new vaccines." Meola reported peptides with viral immunogenic carriers used for immunization.

A "mimotope" means the structure "mimics" some structure of relevance (the relevance determined by the study parameters). A mimotope could be of a chemical nature similar to a native biological structure, or quite different chemically. As an example of the latter, a peptide sequence could be determined from the phage display of peptide sequences that bind to an antibody that was originally produced to a carbohydrate structure (or lipid, or any chemical structurally different from the peptide mimotope). The reason for the latter binding is that, in the universe of chemical structures, many will have the size to "fit" within an antibody combining site and will have atomic compositions capable of forming sufficient non-covalent binding interactions within the antibody combining site to yield a discernible, measurable, assayable affinity.

Thus, discerning a mimotope for any protein binding to selected members of the phage peptide display library as did Meola does not provide the chemical nature of the "natural" binding partner

of the protein. For antibody binding, the natural immunogen structure eliciting the particular antibody, could be quite different than the mimotope peptide structure.

In the Meola report, the mimotopes were selected for study on the basis of having homologous, not identical, sequences to the hepatitis virus surface antigen. Those mimotopes were then conjugated in different ways to several proteins and a MAP platform, used to immunize mice and rabbits, and the immune sera obtained was characterized as to reactivities (antibody binding) to the hepatitis surface antigen. The authors concluded that mimotope identification, followed by preparation of immunogens containing the mimotope sequences, could yield antigens to be used as vaccines possibly effective in protecting individuals against various pathogens. These mimotopes do not have all the elements of claim 1 and they, not HbsAg 120-132, or whatever segment of HbsAg the examiner selects, are what Meola is investigating as target specific antigens.

A. Meola Does not Teach a Peptide of Claim 1

Even assuming that HbsAg is the "target protein" required by claim 1, as the examiner believes, none of the sequences of Meola are identical to "a contiguous amino acid peptide region" of the sequence of the target as they must be to satisfy claim 1(b). (see Meola, Fig. 1) Meola has mimotopes that are not identical to a contiguous sequence of the target protein as required in claim 1(b), "do not show any sequence similarity with the natural Ag" and "show similarity" with 121-127 of HBsAg. "They probably mimic a nonlinear epitope of HbsAg." (page 3169) In fact, Meola teaches away from using a pathogen's primary structure, in contrast to the present invention which starts with the amino acid sequence of the target protein, and derives peptides therefrom.

Referring to disease specific mimotopes, Meola states:

> This information is not readily available by studying the pathogen structure because the immune system reacts to the Ags in a complex way that has to do with presentation and processing.

Meola, page 3162.

A mimotope does not use the linear sequence of pathogen for immunization.

> It became clear that the conformation of the peptide as displayed on the phage is important for immunization.

Meola, page 3163.

Not surprisingly, the exact primary sequence of any 5-10 amino acid contiguous sequences of the hepatitis antigen is not used in the immunization procedures or experiments of Meola, as required in present claim 1(a).

B. There are no "comparative proteins" as required by claim 1(d, e) in Meola;

The examiner decided that:

> Mimotopes 13 and 35 are the selected immunogenic peptides as the **comparative proteins** from phage library. (*emphasis provided, sic)*
>
> (See Office Action page 2, par. 2)

Mimotopes 13 and 35 do not fit the definition of comparative proteins which are selected for present claim 1(d, e), because Meola's mimotopes are all derived from the same HbsAg antigen, whereas comparative proteins of the present invention are from different proteins than a "target protein", and are selected to minimize cross reactivity of antibodies designed to react with the target protein.

What is argued in the Action is the examiner's opinion. Meola never expressly states "comparative protein" nor are mimotopes proteins. Comparative proteins in the pending claims have a different definition: as stated above and in the specification, comparative proteins are selected from some defined set of proteins examined for potential homologies; those with homolgies as defined in claim 1 are then **excluded** in the **claimed** procedures.

C. Definitions

During the interview the examiner requested citations to the specification that supported and/or explored the following terms.

1. Comparative Protein
2. Cross-reactivity
3. Assays in claim 1(f).

1. **Comparative Proteins**

Page	Lines	Comments
2	23 - 28	"non-target proteins"
2 3	35 - 36 1	< 50% homology with the comparative protein (non-target proteins)
	23 - 26	search for all available sequence matches of non-target proteins, select at least one protein that shows some degree of homology to the target protein select amino acid sequences of at least 4 in length
4	20 -25	Step 8 - compare peptides which are 50% or less homologous with peptide regions of comparative protein amino acid sequences
	25 - 29	Step 9 rejects peptides of step 8 with 4 or more contiguous amino acids identical to a contiguous sequence of the comparative proteins
5	5 - 34	Reiterates steps of Claim 1 - "non-target, (non-specific) proteins" are compared. "Functionally specific" peptide antigens are selected on the basis of having no more than 50% amino acid matching (sequence homology) with the comparative protein peptide sequence."
6	7 - 10	"Proteins comprising non-targeted microorganisms, or proteins comprising non-targeted tissues.
10	29 - 34	See also FIGS. 1 and 2.
11	1 - 15	FIG. 1 above where the hydrophilic portion of the sequence of a target protein, are bold and underlined; FIG. 2a shows a comparison between one of those peptides aligned with "closely matched peptide sequence of two comparative microorganism proteins," the comparative proteins were selected by BLAST as "those most closely matching the linear amino acid sequence of the target protein."
11	6 - 15	FIG. 2B shows alignment of target protein sequences with comparative protein sequences (see amended specification).

Those of skill in the art know how to access BLAST (specification, page 2, lines 20-23; page 3, lines 23-26; page 5, lines 13-18; page 10, FIG. 2a; page 12, lines 29-36; page 13, lines 1-2) to search the Protein Data Base for comparative proteins of the present application as instructed in the specification. They would assess the routine in BLAST for "short, nearly exact

matches to the target protein." The results would be inspected to select comparative protein specimens.

2. **Crossreactivity**

Those of skill in the art would understand that the inventor is trying to reduce crossreactivity by use of comparative proteins. (see specification page 2, lines 25-28).

> The reactivity of an antibody with nonhomologous antigens is referred to as *crossreactivity* In Chapter 6, we considered crossreactivity from the standpoint of antibodies; here, we shall briefly discuss crossreactivity in relation to antigens. At the antigen level, crossreactivitiy can occur because of antigen heterogeneity, determinant sharing, or determinant similarity (see Fig. 8.2)

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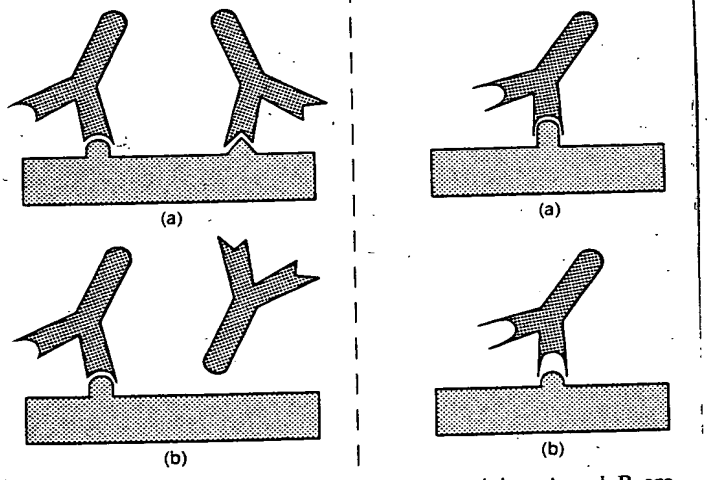

Figure 8.2. Two interpretations of crossreactivity. A and B are antigenic molecules of two inbred strains; the Y-like structures are antibodies. In the left-hand panel, molecule A has two determinants, one of which it shares with molecule B; there are separate antibodies for the two determinants. In the right-hand panel, molecule A has only one determinant; molecule B has a similar, but not identical, determinant, which the antibody fits only imperfectly.

Immunology, the Science of Self-Non-Self-Discrimination, Klein, 1982, John Weley & Sons, Inc.

3. **Assays of Claim 1, Step (f)**

Page	Lines	Comments
4	35 - 50	Describes assays.
6	20 - 28	Describes immunoassays, e.g. "measures specific peptide - reactive antibodies in biological fluids."
7	1 - 13	Diagnostic method
8	32 - 35	"Functionally specific" peptide
9	13 - 19	Definition of "immune response"
11	24 - 36	FIGS. 4 and 5 illustrates a specific use of 1(f) claim and indicate that even if 1(a)-(d) are satisfied, a peptide must satisfy (f), see also Example 1, Page 14
12	30-36	Comparative
13	1-12	proteins show no more than 50% homology with the target - candidate peptides were tested immunologically causing some to be rejected as candidates according to claim 1.

"

D. Mimotopes of Meola are proteins which are larger than 5-10 amino acids because they include viral carriers.

Even if HbsAg sequence 120-132 is a "selected peptide", as the examiner believes, 12 amino acids is outside the scope of claim 1(a).

E. Meola teaches away from peptides of the present claims.

> Thus, the definition of a mimotope, particularly an immunogenic mimotope (i.e., a molecule capable of eliciting Abs to the original Ag it is supposed to mimic), in most cases **cannot be reduced to the description of a short peptide**, leaving aside the molecular context in which it is first identified.

Meola, page 3170 (*emphasis provided*).

III. A Prima Facie Case of Obviousness is not Established Because Rejections Based on Meola are Faulty, Therefore, Meola Must be Removed as a Basis for the 103 Rejections.

Claims 18-19 were rejected under 35 U.S.C. §103(a) over Meola et al in view of Hasegawa et al.

Claim 22 was rejected under 35 USC §103 over Meola and Tu.

Because, as shown in Section II herein, Meola does not teach the peptides of the present invention, these 103 rejections must fall also.

Hasegawa merely teaches adjuvants. There is no teaching or suggestion to combine Meola and Hasegawa. Even if Meola and Hasegawa were combined, the combination does not render claims 18-19 obvious because neither Meola nor Hasegawa teach or suggest a plurality of immunogenic peptides that fits the description of claim 1.

On page 4 of the Action, the examiner states that Meola in view of Tu (US Pat 5674483) renders claim 22 obvious. Tu merely teaches a method of administering IL-12 to reduce inflammation. IL-12 is a "heterodimeric cytokine" exceeding the limits of claim 1 (Howard *et al.* Chap. 20, Fundamental Immunology)

In *Nursery Supplies*, the court held:

> One **cannot simply backtrack from the invention to find a connection** to the prior art. Hindsight must be avoided. See *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). Rather, **one must start with the prior art and find some suggestion or motivation either in a single reference** to modify it to produce the claimed invention, or some suggestion or motivation in a group of references to combine them to produce the claimed invention. *Nursery Supplies v. Lerio Corp.*, 45 U.S.P.Q.2d (BNA) 1332 (M.D. Pa. Sept. 19, 1997). (*emphasis added*).

There is no teaching or suggestion to combine Meola and Tu. Even if Meola and Tu were properly combined, the combination does not produce claim 22 because Meola does not teach or suggest an immunogenic peptides that fit the description of claim 1, and Tu only teaches IL-12.

It is to be noted, however, that citing references which **merely indicate that isolated elements and/or features** recited in the claims are known **is not a sufficient basis** for concluding that the combination of claimed elements would have been obvious. *Ex parte Hiyamizu* (BPAI 1988) 10 PQ. 2d 1393 (*emphasis added*).

Even if all of the elements of a claim are present in the prior art, the claim will not be obvious unless the prior art also contained, at the time the claim was filed, a motivation to combine prior art elements into the claimed invention. The conclusion that the prior art contained a motivation to combine is a conclusion of fact. *Scimed Life Sys. v. Johnson & Johnson*, 2004 U.S. App. LEXIS 510.

Obviousness requires **a suggestion of all limitations** in a claim." *CFMT, Inc. v. YieldupInt'l Corp.*, 2003 U.S. App. LEXIS 23072 (Fed. Cir. 2003) (*emphasis added*).

To properly combine two references to reach a conclusion of obviousness, there must be some teaching, suggestion or inference in either or both of the references, or knowledge generally available to one skilled in the art, which would have led one to combine the relevant teachings of the two references. *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc. et al.* (CAFC 1985) 776 F. 2d 281, 227 USPQ 657; *Ex parte Levengood, supra.* Both the suggestion to make the

claimed composition or device or carry out the claimed process and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure. *In re Vaeck* (CAFC 1991) 947 F. 2d 488, 20 PQ. 2d 1438. The references, viewed by themselves and not in retrospect, must suggest doing what applicant has done. *In re Shaffer* (CCPA 1956) 229 F. 2d 476, 108 USPQ 326; *In re Skoll* (CCPA 1975) 523 F. 2d 1392, 187 USPQ 481.

In *re Rouffet,* the court held

To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court **requires the examiner to show a motivation to combine the references that create the case of obviousness**. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. In *re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). (*emphasis added*).

Therefore, Claims 18-19, and 22 are not obvious over Meola in view of either Hasegawa or Tu.

VI. Conclusion and Summary

In view of the arguments presented herein, please allow all pending claims.

No fees are believed due at this time, however, please charge any additional deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21417/92378).

Respectfully submitted,

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